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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,404	01/04/2002	Sanjay Tyagi	07763-044001	9007

26211 7590 04/20/2004

FISH & RICHARDSON P.C.
45 ROCKEFELLER PLAZA, SUITE 2800
NEW YORK, NY 10111

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,404	TYAGI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The requirement that the loop sequences of the hairpin antisense oligonucleotides being longer than the stem sequence (as stated on page 3, lines 13-20 of the specification as filed) appears to be critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

(a) The instant claims are drawn to an antisense oligonucleotide consisting of a central loop sequence that is complementary to a selected messenger RNA target sequence and that is flanked by 3' and 5' arm sequences that are complementary to one another, wherein in the absence of said target sequence said oligonucleotide assumes an hairpin structure having a double-stranded stem, wherein interaction of said loop sequence with said target sequence causes dissociation of said stem, and wherein interaction of said loop sequence with a sequence complementary thereto except for a single nucleotide does not cause said stem to dissociate. However, the specification as filed provides only one example of the claimed antisense oligonucleotides, specifically the hairpin antisense oligonucleotide having the following sequence: 5'-CGCTGGCCCGCGGCAGCCACACCCCAGCG-3' (SEQ ID NO: 1), where the underlined nucleotides represent the complementary 5' and 3' complementary arms that form a

double-stranded stem in the absence of the target sequence (see page 5 of the specification as filed). The specification as filed discloses certain structural requirements that are not set forth in the claims, and appear to be essential in the design of the hairpin antisense oligonucleotides of the invention. For example, page 3, lines 13-20, of the specification as filed states that "[T]he loop sequences in hairpin antisense oligonucleotides are sufficiently long as compared to the arms such that hybridization of the loop sequence alone drives the opening of the hairpin stem. The length of the loop sequence in a hairpin antisense deoxyriboligonucleotide according to this invention ranges from 7 to 30 nucleotides, preferably 15-25 nucleotides, whereas the length of the arm sequences ranges from 3 to 8 nucleotides, with the loop sequence always being longer than the stem sequence." It appears that these features are essential to the design and function of the claimed hairpin antisense oligonucleotides. Additionally, page 3 of the specification as filed, appears to suggest that if the loop sequences were shorter than the arms, the hairpin antisense oligonucleotide would not function in a highly specific manner.

The specification as filed does not enable the skilled artisan to make the full scope of hairpin antisense oligonucleotides encompassed by the instant claims, specifically wherein said hairpin antisense oligonucleotides comprise stem sequences that are longer than the loop sequence. The specification as filed clearly suggests that those hairpin oligonucleotides that are not designed to comprise wherein the loop sequences are longer than the stem sequences, would not function to discriminate between target sequences that are 100% complementary to said loop sequences and those target sequences that are complementary to said loop sequence except for a single nucleotide. In order to practice the full scope of the claimed invention the skilled artisan would have to resort to trial and error experimentation, without any guidance from the

specification as filed in order to identify those hairpin antisense oligonucleotides according to the claimed invention, wherein the stem sequences are longer than the loop sequences of said hairpin antisense oligonucleotides.

(b) Claim 4 is drawn to a therapeutic method comprising administering to a patient an antisense oligonucleotide according to claim 1.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

The quantity of experimentation required to practice the invention as claimed would require determining the structures of the mRNA targets that are associated with a particular condition or disease, for which therapy is sought. Determining the structures of the highly specific antisense oligonucleotides of the invention, identifying modes of delivery *in vivo* such that the expression of said mRNA target is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully practice a therapeutic method to treat a disease or condition associated with the

expression of a particular mRNA target, comprising the administering to a patient an antisense oligonucleotide according to the present invention. The specification as filed provides only information regarding the ability of the antisense oligonucleotide according to SEQ ID NO: 1 to specifically bind to a mutant carcinogenic form of *ras* mRNA, however there is no evidence that the disclosed antisense oligonucleotide can be used in a therapeutic method to treat cancer in a patient. Furthermore, the instant specification does not provided any clear nexus between binding mutant *ras* mRNA and the general treatment of a patient having any disease or condition associated the expression of any mRNA target.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1999), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins,

oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1999; p. 3). Crooke clearly teaches that there is a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also teach that "Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Moreover, Branch states that "[H]owever, their *(antisense molecules and ribozymes)* unpredictability confounds research applications of nucleic acid reagents."

Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[G]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[A] large number of diverse and talented groups are

working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense based therapeutics, at the time of filing, was unpredictable and those highly skilled in the art working towards making antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

It is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the behavior of antisense oligonucleotides *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a mRNA target, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single nucleic acid target is inhibited and the desired treatment effects are obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

3. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

The instant claims are drawn to an antisense oligonucleotide consisting of a central loop sequence that is complementary to a selected messenger RNA target sequence and that is flanked by 3' and 5' arm sequences that are complementary to one another, wherein in the absence of said target sequence said oligonucleotide assumes an hairpin structure having a double-stranded stem, wherein interaction of said loop sequence with said target sequence causes dissociation of said stem, and wherein interaction of said loop sequence with a sequence complementary thereto except for a single nucleotide does not cause said stem to dissociate. However, the specification as filed provides only one example of the claimed antisense oligonucleotides, specifically the hairpin antisense oligonucleotide having the following sequence: 5'-CGCTGGCCCGCGGCAGCCACACCCCAGCG-3' (SEQ ID NO: 1), where the underlined nucleotides represent the complementary 5' and 3' complementary arms that form a double-stranded stem in the absence of the target sequence (see page 5 of the specification as filed). However, the structure of this highly specific hairpin antisense oligonucleotide can not be used to predict the structure of other hairpin antisense oligonucleotides that would be useful for specific interaction with a 100% complementary target sequence and discriminate in practice against single nucleotide differences in a target sequence. The specification as filed discloses certain structural requirements that are not set forth in the claims, and appear to be essential in the design of the hairpin antisense oligonucleotides of the invention. For example, page 3, lines 13-20, of the specification as filed states that "[T]he loop sequences in hairpin antisense oligonucleotides are sufficiently long as compared to the arms such that hybridization of the loop

sequence alone drives the opening of the hairpin stem. The length of the loop sequence in a hairpin antisense deoxyriboligonucleotide according to this invention ranges from 7 to 30 nucleotides, preferably 15-25 nucleotides, whereas the length of the arm sequences ranges from 3 to 8 nucleotides, with the loop sequence always being longer than the stem sequence." It appears that these features are essential to the design and function of the claimed hairpin antisense oligonucleotides. Additionally, page 3 of the specification as filed, appears to suggest that if the loop sequences were shorter than the arms, the hairpin antisense oligonucleotide would not function in a highly specific manner. Moreover, although this information appears to be critical to the design of the highly specific antisense oligonucleotides of the invention, it is noted that the actual function is identified by experimentation, see the specification as filed that states "[W]hether a particular hairpin antisense oligonucleotide actually exhibits the desired level of specificity can be tested *in vitro* by labeling the hairpin antisense oligonucleotide with terminal interactive labels....and then detecting hybridization by observing the increase in fluorescence intensity (see page 3, lines 22-26)."

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a

variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." Additionally, MPEP § 2163 states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In the instant case, Applicants describe the structure of only one hairpin antisense oligonucleotide, see SEQ ID NO: 1, according to the present invention, wherein said hairpin antisense is capable of discriminating between its 100% complementary target nucleic acid sequences and nucleic acid molecules comprising a single nucleotide difference from its target. However, according to Applicants other highly specific hairpin antisense oligonucleotides according to the present invention must be identified empirically (see page 3, lines 22-26). Without further experimentation, the skilled artisan cannot envision the full scope of highly specific hairpin antisense oligonucleotides encompassed by the instant claims. Therefore, with the exception of the hairpin antisense oligonucleotide according to SEQ ID NO: 1, Applicants were not in possession of the full scope of highly specific hairpin antisense oligonucleotides encompassed by the instant claims.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE